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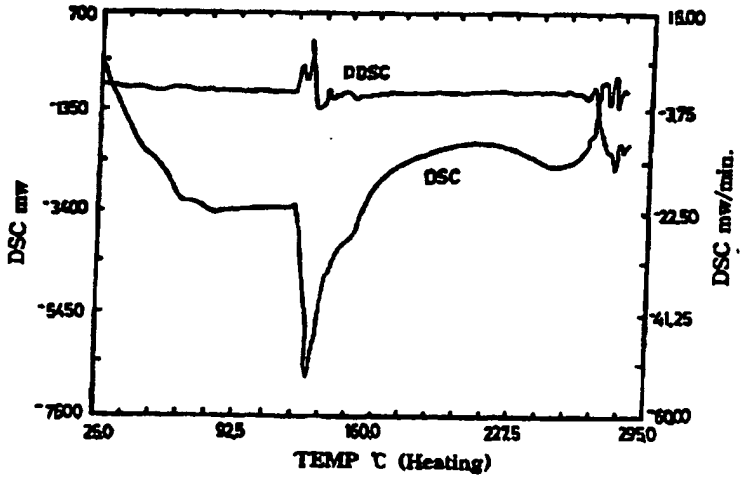

(57) Abstract

The present invention relates to a pharmaceutical composition containing cyclosporin, an oil component, a hydrophilic cosurfactant consisting of propylene carbonate or a mixture of propylene carbonate and polyoxyethylene-polyoxypropylene block copolymer, and a surfactant. The composition of the present invention is characterized in that it can be dissolved in an external phase such as water, artificial gastric juice and intestinal juice, etc. to form a self-emulsion with mild stirring and therefore, by appropriately adjusting the constitutional ratio of each component the diameter of particles in the inner phase of the emulsion thus formed can be readily controlled to 100 nm or below. The composition of the present invention can be formulated into the oral preparations such as soft capsules, hard capsules sealed with gelatin bending at the conjugated portion, oral liquid preparations, etc.

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CYCLOSPORIN-CONTAINING PHARMACEUTICAL COMPOSITION

TECHNICAL FIELD

The present invention relates to a pharmaceutical composition containing cyclosporin. More specifically, the present invention relates to a pharmaceutical composition containing cyclosporin, an oil component, a hydrophilic cosurfactant consisting of propylene carbonate or a mixture of propylene carbonate and polyoxyethylene-polyoxypropylene block copolymer, and a surfactant. The composition of the present invention is characterized in that it can be dispersed with mild stirring in an external phase such as water, artificial gastric juice and intestinal juice, etc. to form a self-emulsion. The diameter of particles in the inner phase of the emulsion thus formed can be readily controlled to 100㎚ or below by adjusting the constitutional ratio of each component.

BACKGROUND ART

Cyclosporin is a high molecular peptide compound (molecular weight 1202) consisting of 11 amino acids which achieves its potent immunosuppressive activity by inhibiting the growth and differentiation of T cells. Therefore, cyclosporin has been used for suppressing immunological rejection caused by organ and tissue transplantation, for example, transplantation of kidney, liver, heart, bone marrow, pancreas, skin, cornea, etc. Cyclosporin has also been used for suppressing autoimmune diseases, especially inflammatory diseases such as rheumatoid arthritis.

Cyclosporin has a unique structure, in which seven of its 11 amino acids are in N-methylated form. In addition, cyclosporin, which has a cyclic, symmetric structure, has a very low polarity and therefore, is only slightly soluble in water (0.04㎎/㎖ H_2O, 25℃). Due to such a low water-solubility of cyclosporin, the bioavailability of cyclosporin may be 30% or less. The absorption of such an insoluble compound may be

greatly influenced by bile juice secreti ns and the amount of fat in food. In the case of cyclosporin, it has been reported that differences in absorption between individuals are as great as about 5-50%.

When cyclosporin is administered, 10 to 27% of the absorbed drug is subjected to the first pass effect in liver and the distribution half-life ranges from 0.7 to 1.7 hour and the excretion half-life ranges from 6.2 to 23.9 hours. Such pharmacokinetic parameters of cyclosporin clearly show great variation among individuals depending on the patient's secretion of bile juice, the condition of the patient and the organ transplanted. In addition, cyclosporin has a very low therapeutic index and frequently shows renal toxicity as a typical side effect. That is, cyclosporin shows renal side effects such as a reduction of glomerular filtration, and an increase in proximal renal tubular reabsorption, etc. A form of chronic progressive cyclosporin-associated nephrotoxicity is characterized by serial deterioration in renal function and morphologic changes in the kidney. Therefore, in USA cyclosporin is classified as a member of the group of drugs which are subject to periodic therapeutic drug monitoring (TDM).

Since cyclosporin has such specific properties, that is, a very slight solubility, a low bioavailability and a great variation in absorption among individuals, a large dosage unit and a narrow therapeutic index, and the unstable condition of patient to be treated with cyclosporin, it is very difficult to establish an optimum drug dosage regimen for survival of transplanted patient by maintenance of efficient and constant blood concentration which can avoid side effects and rejection. Numerous studies have been conducted to develop an improved pharmaceutical formulation. Such studies have mainly concentrated on means which be used to solubilize cyclosporin. Typical examples include the use of liposome, microspheres, or mixed solvent systems consisting of general vegetable oil and surfactant, and the formation of powdery composition using adsorption, inclusion complexes, solid dispersions, etc., and the other numerous formulations.

An oral preparation containing cyclosporin as the primary active ingredient has been commercialized in solution form or a soft capsule formulation. Recently, a microemulsion preconcentrate composition containing cyclosporin has been commercialized in a soft capsule formulation.

Microemulsions were first reported by J. H. Schulman in 1943 and have, since then, been mainly studied as carriers for application of cosmetics. A microemulsion which is a thermally stable and optically transparent preparation comprising two or more immiscible systems formed by surfactants, has the advantages of very low surface tension and small particle size, which together result in high absorption and permeation properties. However, since formation of a microemulsion requires more surfactant than is used for formation of a general emulsion, when microemulsion is administered to a patient for a long period, mucosal irritation caused by each component must be considered. In medical field, microemulsions have thus been utilized only for preparations which are applied to the skin for only short periods such as preparations for hair, detergents, etc.

According to the optimum water-in-oil microemulsion disclosed in U. S. Serial No. 818,965, it is described that when the microemulsion is prepared by selecting the surfactant and the cosurfactant which is more hydrophilic than the surfactant, and then adding the surfactant and the oil component to the external phase in which the cosurfactant is dissolved, the transparent microemulsion can be efficiently obtained under more stable and variable conditions. This patent also reports a microemulsion preconcentrate formulation prepared by dissolving the slightly soluble drug in a hydrophilic cosurfactant, such as small chain hydrocarbons, mixing the drug solution thus obtained with the oil component and adding the surfactant to the external phase.

In the case of cyclosporin as the very slightly soluble drug, U.S. Patent No. 4,388,307 discloses an oral liquid preparation which includes oil, surfactant, and ethanol as the hydrophilic solvent. This preparation is

a microemulsion preconcentrate and, th refore, must be diluted with water before it is administered orally. Accordingly, it is very difficult to adapt the subject patient to its administration and to control the dosage and as a result, it is impossible to actually administer to a patient who must undergo cyclosporin therapy for the rest of his life since it is uncomfortable to carry.

In order to mitigate the disadvantages of liquid preparations, it has been proposed that the microemulsion preconcentrate is formulated in the form of soft capsules. However, in case of the cyclosporin soft capsule containing ethanol as its hydrophilic component, this capsule preparation must contain a large amount of ethanol to solubilize the cyclosporin. However, since ethanol permeates the gelatin shell of the capsule to volatilize even at normal temperature, the content of ethanol is reduced in course of time. As a result, when the capsules are stored at high temperatures or at normal temperatures for long period, the crystallization of cyclosporin may be caused. Thus, the change in constitutional ratio of the composition caused by the change of ethanol content and the crystallization of cyclosporin result in a great variation in the bioavailability of cyclosporin and therefore, it is almost impossible to obtain a desired therapeutic effect. In an effort to prevent the volatilization of ethanol from the soft capsule preparations during storage, the soft capsule preparations are often enclosed in a special packaging material, such as aliminum-aluminum blister packaging. However, such special packaging does not completely prevent the change of ethanol content in course of time. Therefore, this also results in a great variation in bioavailability of cyclosporin and may contribute to an increase in the manufacturing price increase.

To mitigate the above-mentioned disadvantages of the use of ethanol as hydrophilic cosurfactant a method using non-ethanol component as hydrophilic cosurfactant has also been proposed. U.S. Patent No. 5,342,625 discloses the soft capsule preparation formulated from microemulsion concentrate which solves the above-mentioned problems. In this patent, a pharmaceutical composition in the form of microemulsion

concentrate in which a pharmaceutically acceptable C_{1-5} alkyl or tetrahydrofurfuryl di- or partial-ether of a low molecular mono- or poly-oxy-alkanediol, for example, diethyleneglycol monoethyl ether [e.g. Transcutol] or tetrahydrofurfurylalcohol polyethylene glycol [e.g. Glycofurol], or 1,2-propylene glycol is used as a hydrophilic cosurfactant and ethanol is used as a hydrophilic co-solvent is disclosed. However, all the hydrophilic cosurfactants used in this patent are glycols having the alcoholic group (-OH) in their structure. Since such -OH group containing glycols are very hygroscopic, they absorb moisture present in atmosphere and further have a high permeability to gelatin shell. Therefore, it is very difficult to formulate a composition containing such a glycolic cosurfactant into a soft capsule preparation. Particularly, in encapsulating and drying procedures during the preparation of soft capsules water present in the capsule shell is absorbed into the capsule contents by 20% of the amount of the hygroscopic solvent to cause the change in constitutional ratio of the composition and then in drying procedure water is distributed again into the gelatin shell together with the constituents of the composition and volatilized through the outer capsule shell. According to this, the composition of this patent has disdvantages that the initial constitutional ratio of the composition is greatly changed to cause the change in the appearance of the preparation and also the decrease in production yield.

Furthermore, since the solvent used in the formulation disclosed by the above U.S. patent softens the gelatin shell, this composition has the problem that the stability of the appearance of the gelatin capsule is greatly reduced. This problem becomes even more serious when the solvent used is also a plasticizer for gelatin, for example, propylene glycol or glycerin. For this reason, the use of propylene glycol as the main solvent is almost impossible. Specifically, propylene glycol is used generally by approximately 5% of the capsule contents and may be used by approximately 10% together with a hardening agent for gelatin shell at the most. When the content of propylene glycol exceeds 10%, the stability of appearance of the gelatin shell is greatly affected.

As one method for mitigating such disadvantages, Korean Patent Application No. 94-13945 discloses a cyclosporin soft capsule composition (trade name : Neoplanta®) that uses dimethylisosorbide as the hydrophilic cosurfactant. Since dimethylisosorbide used as the hydrophilic solvent has substantially no permeability to the gelatin shell in comparison to the hydrophilic cosurfactants used in the prior art, the soft capsule preparation using dimethylisosorbide provides some advantages that it does not show the change in appearance of the capsule and content of the ingredients.

Dimethylisosorbide which is marketed under the trade name Arlasolve®, i.e., 1,4:3,6-dianhydro-2,5-dimethyl-D-glucitol, a solvent which has been generally used as a percutaneous absorption promoting agent only for topical pharmaceutical ointments or cosmetics such as lotions.

As mentioned above, a conventional microemulsion requires more surfactant than a general emulsion and therefore, in the case of a drug which is continuously administered to the patient during his whole life after transplantation, for example, cyclosporin, the toxicity due to long term administration of solvent and surfactant used in the preparation of the microemulsion must be considered. In this connection, the LD_{50} value of each surfactant used in cyclosporin formulations in the prior art is as follows: dimethylisosorbide 5.63㎖/㎏ (rat, per oral), Cremophor RH40 >16g/㎏ (rat, per oral), Glycofurol 3.5㎖/㎏ (mouse, intravenous injection) and propylene glycol 21-33.7g/㎏ (rat, per oral). In case of the organic solvent of which the toxicity has been relatively well known, the LD_{50} value of each solvent is as follows: acetonitrile 3.8g/㎏ (rat, per oral), acetone 10.7㎖/㎏ (rat, per oral), benzene 3.8㎖/㎏ (rat, per oral), toluene 7.53g/㎏ (rat, per oral), isopropanol 5.8g/㎏ (rat, per oral), butanol 4.36g/㎏ (rat, per oral), and propylene carbonate, which is used in the present invention 29g/㎏. In view of the above LD_{50} values, the toxicity of dimethylisosorbide is relatively high as much as the toxicity of general organic solvents and therefore, it is expected that the long term oral administration of the composition containing dimethylisosorbide may cause problems. Furthermore, according to this patent dimethylisosorbide is

used in an amount 4 times as much as cyclosporin on the basis of weight. This must be seriously considered in view of the fact that this drug is administered to the patient through his whole life.

In addition, in case of the cyclosporin soft capsule composition using dimethylisosorbide, it is disadvantageous that to obtain the comparable drug absorption to the commercial product Sandimmun Neoral® and a solubilizing effect sufficient to prevent the precipitation of cyclosporin the solvent is used in a relatively larger amount than the active ingredient. This means an increase in the unit dosage. That is, the hydrophilic cosurfactant, i. e. dimethylisosorbide is used in the 4 times amount per unit weight of cyclosporin. Therefore, the total weight of the unit dosage form of Neoplanta® capsule containing 100㎎ of cyclo- sporin is about 1270㎎ which is about 1.2 times as much as the weight of unit dosage form of the prior art formulation (Sandimmun Neoral®). In addition, the price of dimethylisosorbide is 20 to 30 times as high as the price of the solvents used in prior art formulations to cause an increase in the cost of materials of the preparation and thus the price of drug.

The present inventors have long studied cyclosporin preparations that uses various combinations of hydrophilic cosurfactants, oils and surfactants in view of their stability and bioavailability to prepare the cyclosporin-containing composition which compensates for the disadvantages involved in the various pharmaceutical preparations of the prior art and is suitable for the formulation into the soft capsule and to establish the reliable drug dosage regimen with low toxicity and small dosage unit. We have identified that when as the hydrophilic cosurfactant in the cyclosporin-containing composition propylene carbonate, which is a pharmaceutically acceptable solvent, or a mixture of propylene carbonate with polyoxyethylene-polyoxypro- pylene block copolymer in a liquid state at room temperature is used, the above-mentioned requirement can be satisfied and the disadvantages exhibited by the prior art preparations can also be mitigated, and thus completed the present invention.

An object of the present invention is to provid a cyclosporin-containing pharmaceutical composition that comprises cyclosporin; propylene carbonate or a mixture of propylene carbonate and polyoxyethylene-polyoxypropylene block copolymer as a hydrophilic cosurfactant; an oil component; and a surfactant.

Another object of the present invention is to provide a soft capsule preparation, a hard gelatin capsule preparation sealed with gelatin bending at the conjugated portion and an oral liquid preparation, all three prepared from the cyclosporin-containing pharmaceutical composition defined above.

The foregoing has outlined some of the more pertinent objects of the present invention. These objects should be construed to be merely illustrative of some of the more pertinent features and applications of the invention. Many other beneficial results can be obtained by applying the disclosed invention in a different manner or modifying the invention within the scope of the disclosure. Accordingly, other objects and a more thorough understanding of the invention may be had by referring to the disclosure of invention and the drawings, in addition to the scope of the invention defined by the claims.

BRIEF DESCRIPTION OF DRAWINGS

For a thorough understanding of the nature and objects of the invention, reference should be had to the following detailed description taken in connection with the accompanying drawings in which:

Figure 1 is a DSC and DDSC graph of the shell of soft gelatin capsule in which mineral oil is filled, after storage for 3 months according to Experiment 1;

Figure 2 is a DSC and DDSC graph of the shell of soft gelatin capsule in which propylene glycol is filled, after storage for 3 months according to Experiment 1;

Figure 3 is a DSC and DDSC graph of the shell of soft gelatin capsule in which propylene carbonate is filled, after storage for 3 months according to Experiment 1; and

Figure 4 is a graph showing the cyclosporin level in whole blood after administration of the cyclosporin-containing pharmaceutical composition prepared according to the present invention (test preparation) in comparison with that of the commercial cyclosporin preparation (Sandimmun Neoral® : comparative preparation), in which ●-● denotes the cyclosporin level in whole blood after administration of the comparative preparation and ■-■ denotes the cyclosporin level in whole blood after administration of the test preparation.

DISCLOSURE OF INVENTION

The present invention relates to a cyclosporin-containing pharmaceutical composition that comprises cyclosporin; propylene carbonate or a mixture of propylene carbonate and polyoxyethylene- polyoxypropylene block copolymer as a hydrophilic cosurfactant; an oil component; and a surfactant. This composition solves various problems exhibited by the prior art compositions when it is formulated in the form of soft capsules.

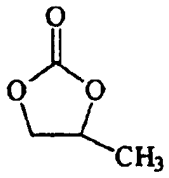
More specifically, the present invention relates to a pharmaceutical composition that includes: (1) as its active ingredient, cyclosporin; (2) as its hydrophilic cosurfactant, propylene carbonate or a mixture of propylene carbonate and polyoxyethylene-polyoxypropylene block copolymer which is a liquid at room temperature; (3) as its oil component, one of medium chain triglyceride and mono- and di-glyceride or a mixture thereof; and (4) a surfactant.

The first essential component of the pharmaceutical composition according to the present invention is cyclosproin as an active ingredient. Cyclosporin is a cyclic peptide compounds which consists of 11 amino acids and exhibits a pharmacologically useful activity, i. e. immunosuppresive activity. Although cyclosporin A, B, C, D or G

depending on the structure of constituent amino acids may be used as the cyclosporin component in the present invention, cyclosporin A is preferred, since its pharmacological activity and clinical indication and effectiveness are well established in the art.

The second essential component of the composition of the present invention is a hydrophilic cosurfactant. The hydrophilic cosurfactant, which can be used in the cyclosporin-containing pharmaceutical composition of the present invention, includes propylene carbonate or a mixture of propylene carbonate and polyoxyethylene-polyoxypropylene block copolymer in a liquid state at room temperature.

One of the cosurfactants which may be used in the present invention, propylene carbonate is a colorless transparent liquid and has the chemical name (±)-4-methyl-1,3-dioxolan-2-one. It has been often used as a solvent for the pharmaceutical preparations for oral and topical administration. The chemical structure of propylene carbonate is represented by the following formula (I) :



(I)

Propylene carbonate is often used as a non-volatile, stable liquid carrier, especially in hard gelatin capsule preparations. Since it has a boiling point of 242℃, propylene carbonate does not volatilize during storage at normal temperatures or during preparation of the soft capsules at high temeperatures and therefore, helps to ensure the stability of the preparation during both storage and production. Further, since propylene carbonate does not contain a hydroxy group (-OH), it does not exhibit serious hygroscopicity in marked contrast with glycols, and also does not permeate the gelatin capsule shell. Due to the good solubility of

cyclosporin in propylene carbonate for very slightly soluble drug, it can be readily applied to cyclosporin.

Another substance which can be used together with propylene carbonate as the hydrophilic cosurfactant in the composition of the present invention is polyoxyethylene-polyoxypropylene block copolymer which is liquid at room temperature. Such block copolymer has been commercialized under the trade name Pluronic L10, L31, L35, L43, L101, 31R1 and Poloxamer 124, with Poloxamer 124 which is pharmaceutically acceptable being preferably used as the mixture with propylene carbonate. Poloxamer 124 is also available under trade name Lutrol or Pluronic L44 and Synperonic PE L44. Poloxamer is a hydrophilic, high molecular surfactant having molecular weight of 2000 to 18000, which may be used as a solvent for medicinal components, lipid emulsions, ointment base, binders or coating agents for tablets, gelling agent, etc. Although the properties of poloxamers depend on their series, they are thermally stable with a flash point of 260℃. Poloxamer 124 dissolves easily in organic solvents such as propylene glycol or xylene, in contrast to other poloxamers. In addition, in comparison with all other solvents used in prior art cyclosporin formulations, poloxamer is not hygroscopic. It thus does not change the constitutional ratio by dissolution of gelatin shell, permeation or evaporation.

As the cosurfactant in the present invention, either propylene carbonate alone or a mixture of propylene carbonate and polyoxyethylene-polyoxypropylene block copolymer in a liquid state at room temperature can be used. When a mixture of propylene carbonate and polyoxyethylene-polyoxypropylene block copolymer in a liquid state at room temperature is used as the hydrophilic copolymer in the present invention, they may be combined in the ratio of 1:0.1-5, preferably 1:0.1-3, more preferably 1:0.1-1, on the basis of weight.

In the cyclosporin-containing pharmaceutical composition according to the present invention, the ratio of the hydrophilic cosurfactant to cyclosporin is preferably in the range of 1:0.5-5, more preferably 1:1-3, on the basis

of weight.

The use of the above-defined hydrophilic cosurfactant selected according to the present invention in the cyclosporin-containing preparation can provide a solubilizing effect sufficient for cyclosporin and also provide some advantages that the cosurfactant thus selected neither changes the capsule's appearance nor cause precipitation of the active ingredient cyclosporin depending upon solvent content. It reduces the cost of manufacturing to provide an economical effect and does not have any toxicity problem of the solvent.

The third essential component contained in the composition of the present invention is an oil component. In the composition of the present invention, any one of medium chain triglyceride and mono- and di-glyceride or a mixture thereof can be used as the oil component.

As the medium chain triglyceride in the oil component a triglyceride of a saturated fatty acid having 8 to 10 carbon atoms may be used. Such a medium chain triglyceride provides many advantages over general vegetable oils. Since medium chain triglycerides have low sensitivity to oxidation and densities of 0.94-0.95, which is higher than that of vegetable oils and near to that of water, an emulsion using a medium chain triglyceride oil component is more stable than a general emulsion. In addition, such a medium chain triglyceride is less hydrophobic than vegetable oils and it solubilizes the active ingredient between than general oil components. Therefore, when the composition of the present invention is prepared using such medium chain triglyceride, it is possible to obtain a higher concentration of the active ingredient without a significant increase in the viscosity of the composition. This means that the medium chain triglyceride is an oil very suitable to the drug of which the dose is great such that the concentration of active ingredient to carrier is as high as 10% and which has very low polarity and therefore, is very slightly soluble in water, for example, cyclosporin. Such a medium chain triglyceride has been commercialized under the trade names Sefol 860, Sefol 870, Sefol 880, Miglyol 810, Miglyol 812 and Miglyol

818.

As another oil component, a mono- and di-glyceride may be used. A mono- and di-glyceride is a mixture of glycerol mono- and di-esters of a fatty acid in which the ratio of monoglyceride to diglyceride is at least 40%. In order to control the absorption of cyclosporin, it is preferable that the mono- and di-glyceride contain a monoglyceride of C_{18} fatty acid as its main component. Such a compound has been commercialized under the trade name GMO AV1 (Croda Co.), ATMOS 300 (ICI Co.), GMOrphic-80 (Eastman Co.), etc.

In the composition of the present invention, any one of the above oils alone or in combination may be used as the oil component. When a mixture of medium chain triglyceride and mono- and di-glyceride is used as the oil component, they should be present in the mixing ratio of 1:0.1-1, preferably 1:0.1-0.5, on the basis of weight.

In the pharmaceutical composition of the present invention, the constitutional ratio of the oil component to cyclosporin is preferably 1:0.5-5 and preferably 1:1-3, on the basis of weight.

The fourth essential component in the cyclosporin-containing pharmaceutical composition according to the present invention is a surfactant. Any pharmaceutically acceptable surfactant may be used, provided it is miscible with both the oil and the hydrophilic cosurfactant components to form an emulsion under mild stirring in the external phase and can adjust the particle diameter in the inner phase to 100㎚ or below by controlling the constitutional ratio thereof. Surfactants which may be used for this purpose include polyoxyethylene glycolated natural or hydrogenated vegetable oils, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene fatty acid esters, polyoxyethylene alkyl ethers, polyethylene glycol mono- and di-fatty acid esters, transesterification product of natural vegetable oil triglyceride with polyalkylene polyol, etc. More preferable surfactant is polyethylene glycol mono- and di-fatty acid esters commercialized under the trade name Solutol (BASF),

polyoxyethylene sorbitan fatty acid esters comm rcialized under trade name Tween (Lippo Chem.), the reaction product of castor oil and ethylene oxide commercialized under the trade name Cremophor (e.g. Cremophor RH60, RH40, EL, etc., BASF), transesterification product of natural vegetable oil triglyceride and polyalkylene polyol commercialized under the trade name Labrafil (e.g. Labrafil M1944 CS, M2125 CS, WL 2609 BS, Labrafac CM-10, Labrasol, Etablissement Gattefosse). One or more selected from the group consisting of polyoxyethylene glycolated natural or hydrogenated vegetable oils and transesterification products of natural vegetable oil triglyceride and polyalkylene polyol are preferably used as the surfactant. If a mixture of polyoxyethylene glycolated natural or hydrogenated vegetable oils and transesterification products of natural vegetable oil triglyceride and polyalkylene polyol is used as the surfactant, these components should be present in the mixing ratio of 1:0.1-1, preferably 1:0.1-0.5, on the basis of weight.

In the composition of the present invention, any one of the surfactants alone or a mixture of any two or more of them may be used as the surfactant. In the present invention, the constitutional ratio of the surfactant to cyclosporin is 1:1-7, preferably 1:3-7, on the basis of weight.

As mentioned above, in the composition of the present invention polyoxyethylene-polyoxypropylene block copolymer which is in a liquid state at room temperature and has an emulsifying property, in combination with propylene carbonate can be used as the hydrophilic cosurfactant. As previously described, it was already disclosed that when the microemulsion is prepared using the surfactant and the cosurfactant having more hydrophilic property than the surfactant, the microemulsion can be produced under various conditions and the microemulsion thus produced has an excellent stability. The composition of the present invention uses as the hydrophilic cosurfactant poloxamer 124 which is more hydrophilic than the surfactant, so that the surfactant and cosurfactant together form a microemulsion. The prior preparations used ethanol, propylene glycol, transcutol, glycofurol, dimethylisosorbide,

etc. which acted merely as the solvent and have practically no emulsifying property. Therefore, the cyclosporin-containing pharmaceutical composition according to the present invention can form a more advantageous and stable microemulsion under the patient's variable gastro-intestinal conditions in comparison to the microemulsion preconcentrates of the prior art.

In the composition according to the present invention, four essential components should be present in the ratio of cyclosporin : hydrophilic cosurfactant : surfactant : oil component = 1 : 0.5-5 : 1-7 : 0.5-5, and preferably in the ratio of cyclosporin : hydrophilic cosurfactant : surfactant : oil component = 1 : 1-3 : 3-7 : 1-3, on the basis of weight. In addition to this composition, the composition illustrated in the following examples can be mentioned as the further preferable compositions according to the present invention.

The cyclosporin-containing pharmaceutical composition according to the present invention may further contain conventional pharmaceutically-acceptable additives as needed. Such additives include anti-oxidants (e.g., tocopherol, BIIA), viscosity regulators, releasing regulators, perfumes (e.g., peppermint oil), preservative (e.g., benzylalcohol, parabens), and coloring agents, etc.

For clinical use, the composition of the present invention may be formulated into oral preparations such as soft capsules, hard capsules sealed with gelatin bending at the conjugated portion, oral liquid preparations, etc., using pharmaceutically acceptable additives according to conventional method in the pharmaceutical field. For example, when the composition of the present invention is formulated into soft capsules, according to the conventional method for preparing soft capsules it can be prepared, for example, by first dissolving cyclosporin in the hydrophilic cosurfactant under mild warming, adding the oil component and the surfactant to the resulting solution, uniformly mixing the constituents, then, if necessary, adding pharmaceutically acceptable additives, and finally formulating the resulting mixture into soft capsules

by means of a machine for preparing soft capsules.

Particularly, when the composition according to the present invention is formulated into soft capsules, the soft capsules thus prepared yield blood level of cyclosporin which are comparable to those obtained by commercial cyclosporin soft capsules and further, do not exhibit any change of composition with time due to volatilization and permeation of the constituents, and reduces the toxicity of solvent, which may make a problem in long-term therapy. The composition of the present invention thus represents an improvement over cyclosporin soft capsules of the prior art.

The present invention will be more specifically illustrated by the following examples, but is not limited by these examples in any manner.

Example 1 (Cyclosporin capsule for oral administration)

Component	Content (㎎/500㎎ Cap.)
Cyclosporin	50.0
Propylene carbonate	120.0
Cremophor RH40	250.0
Miglyol 812	80.0

50g of Cyclosporin was dissolved in 120g of propylene carbonate with stirring and heating. The given amounts of oil component and Cremophor RH40 were added to the mixture thus obtained, which was stirred until a homogeneous solution was formed. The resulting cyclosporin-containing composition was poured to a machine for preparing soft capsules and then encapsulated according to conventional methods for producing soft capsules. Each capsule contained 50㎎ of cyclosporin. Alternatively, after the cyclosporin-containing composition was prepared as described above, the composition was filled in hard gelatin capsules and the conjugated portion of the hard capsules was sealed with gelatin bending to produce hard capsules containing 50㎎ of cyclosporin per capsule.

Example 2 (Cyclosporin soft capsule for oral administration)

The soft capsule preparations of Examples 2-A to 2-C, having the compositions given in the following Table 1, were prepared using propylene carbonate alone or in combination with polyoxyethylene-polyoxypropylene block copolymer which is a liquid at room temperature as the hydrophilic cosurfactant according to the method of Example 1.

Table 1

Example No. / Constituent	2-A (mg/Cap.)	2-B (mg/Cap.)	2-C (mg/Cap.)
Cyclosporin	50.0	50.0	50.0
Propylene carbonate	100.0	70.0	100.0
Lutrol L44			25.0
Pluronic L121		45.0	
Cremophor RH40	210.0		175.0
Labrafil	20.0	195.0	25.0
GMOrphic 80	35.0	25.0	35.0
Sefol 880	100.0	150.0	90.0
Total	515.0	535.0	500.0

Example 3 (Cyclosporin soft capsule for oral administration)

The soft capsules of Examples 3-A to 3-C, having the composition given in the following Table 2, were prepared using any one of a medium chain triglyceride or mono- and di-glyceride or a mixture of the two as the oil component according to the method of Example 1.

Table 2

Constituent \ Example No.	3-A (mg/Cap.)	3-B (mg/Cap.)	3-C (mg/Cap.)
Cyclosporin	50.0	50.0	50.0
Propylene carbonate	100.0	120.0	120.0
Synperonic PE L44	40.0		
Cremophor RH40	250.0	230.0	225.0
GMOrphic 80	60.0	130.0	
Sefol 880	100.0		120.0
Total	600.0	530.0	515.0

Example 4 (Cyclosporin soft capsule for oral administration)

The soft capsule preparation was prepared with the addition of pharmaceu- tically acceptable additives to the composition of the present invention according to the method of Example 1.

Component	Content (mg/ Cap.)
Cyclosporin	50.0
Propylene carbonate	120.0
Miglyol 880	100.0
Solutol HS15	230.0
Tocopherol	1.5
Total	501.5

Example 5 (Cyclosporin solution for oral administration)

Component	Content (mg)

Cyclosporin		100.0
Propylene carbonate	250.0	
Poloxamer 124		50.0
Cremophor RH40		400.0
Labrafil		200.0
Sefol 880		200.0
ATMOS 300		100.0

According to the same method as Example 1, cyclosporin was dissolved and then filled in a suitable container. Before this solution was administered, it was diluted with water.

The stability and pharmacological effect of the cyclosporin-containing pharmaceutical composition produced by using propylene carbonate and poloxamer 124 as the hydrophilic cosurfactant according to the present inventon were determined according to the following experiments and compared with those of the prior art preparations.

Experiment 1

Test for the reactivity of the hydrophilic cosurfactant according to the present invention with the gelatin shell in comparison to the reactivity of the solvents used in the prior art using a thermoanalyzer:

The reactivity of the hydrophilic cosurfactant used according to the present invention and propylene glycol used as the hydrophilic cosurfactant in the prior art preparations with the gelatin shell were determined using a thermoanalyzer.

Each of the hydrophilic cosurfactants and mineral oil as the control solvent was filled in the soft gelatin capsule. The filled capsules were stored at room temperature. At regular intervals, the capsules were cut open with a sharp open blade, and the contents of the capsules were removed by washing with ether and then about 20㎎ of gelatin shell was accurately weighed and analyzed. The programed heating rate was 10℃

/minute under nitrogen purge from 25℃ to 300℃.

The variable DSC and DDSC curves depending on temperature were depicted in Figures 1 to 3. Upon comparing the result of thermal analysis for each solvent with the DSC result of gelatin shell of the soft capsule filled with mineral oil, it can be seen that propylene glycol shows a new peak which demonstrates that the reaction of the hydrophilic cosurfactant with the gelatin shell occurs concurrently with the distribution due to the permeation of the hydrophilic cosurfactant into the gelatin shell, and its DSC curve is greatly varied between 25℃ and 100 ℃. However, in the thermal analysis the hydrophilic cosurfactant according to the present invention shows substantially same thermal analysis pattern as the shell of gelatin capsule filled with mineral oil.

From this result, it can be noted that contrary to the hydrophilic cosurfactant used in the prior art since the hydrophilic cosurfactant used in the present invention does not occur the reaction and distribution with gelatin shell and therefore, does not cause the change in the contents of the composition, it is a solvent suitable for the soft capsule preparation. Therefore, it is apparent that the preparation produced by using such cosurfactant component according to the present invention is superior to the prior art preparations with respect to stability and reliability on the pharmacological effect.

<u>Experiment 2</u>

Change with time of the constitutional ratio due to volatilization of the solvent and Comparison of the stability of the preparations influenced by such changes of the constitutional ratio:

The change in the constitutional ratio of the composition due to volatilization of the hydrophilic component during storage after the soft capsule is prepared, and the stability of the preparation influenced by these changes in the constitutional ratio of the composition were determined. In this test, the cyclosporin-containing preparation using

propylene carbonate and poloxamer 124 as the hydrophilic cosurfactant according to the present invention was used as the test preparation and the prior art preparation produced by using ethanol as the cosurfactant according to the prior art (Sandimmun Neoral®) was used as the comparative preparation.

The conditions for storage were as follows: The test preparation and the comparative preparation were each packed in bottles and aluminum foil packing and each package was stored under three kinds of conditions, i.e. 35℃, relative humidity 75%/35℃, and drying condition/ normal temperature, resepctively. The change in the content of ethanol and propylene carbonate in each preparation was then measured and compared. The content of propylene carbonate was measured by HPLC and the content of ethanol was measured by GC after pretreatment of the aliquot of the contents of the composition. The conditions for analysis are as follows:

A) Propylene carbonate

Apparatus : Waters HPLC system, Mobile phase : water/methanol= 9:1(v/v), Flow rate : 1.0㎖/min., Column : Zobax ODS column, Internal standard : resorcinol, Injection volume : 100㎕, Detection wavelength : 190㎚

B) Ethanol

Pretreatment : Aliquot of the contents of the composition was separated and 30㎖ of chloroform was added thereto. The mixture was sonificated for 15 minutes and then 20㎖ of chloroform was added and thoroughly mixed.

Analysis : Column : Porapak Q (100-120 mesh, length : 1m), Column temperature : 135℃, Detector : FID (temperature : 200℃), Injection temperature : 150℃, Carrier gas : N_2 gas (0.65kg/㎠), air (0.8kg/㎠), Injection volume : 5㎕, Internal standard : diethylether

The test results are given in the following Tables 4 and 5.

Table 4

Change in the content of hydrophilic cosurfactant of the test preparation and the comparative preparation (bottle package)

Preparation	Storage condition	Change in the content of hydrophilic cosurfactant (㎎/Cap.)				
		0	1 mon.	2 mon.	4 mon.	8 mon.
Comparative preparation (ethanol)	35℃, RH75%	62.18	48.2	35.0	18.1	1.35
	35℃, drying		52.1	46.7	40.4	26.2
	normal temperature		59.2	57.0	54.8	48.41
Test preparation (propylene carbonate)	35℃, RH75%	102.0	99.8	97.9	97.2	96.4
	35℃, drying		101.2	100.5	99.4	97.2
	normal temperature		103.0	101.2	99.5	98.5

Table 5

Change in the content of hydrophilic cosurfactant of the test preparation and the comparative preparation (aluminum foil package)

Preparation	Storage condition	Change in the content of hydrophilic cosurfactant (㎎/Cap.)				
		0	1 mon.	2 mon.	4 mon.	8 mon.
Comparative preparation (ethanol)	35℃, RH75%	62.18	56.3	50.7	47.1	35.1
	35℃, drying		60.5	58.7	55.1	49.1
	normal temperature		61.0	59.8	58.1	56.4
Test preparation (propylene carbonate)	35℃, RH75%	102.0	101.5	100.5	98.7	99.3
	35℃, drying		100.3	101.5	99.8	98.9
	normal temperature		101.8	101.4	101.5	101.3

From the results given in the above Tables 4 and 5, it can be noted that the initial concentration of hydrophilic cosurfactant in the test preparation was essentially unchanged during the 8 month test period. In contrast, the comparative preparation shows a dramatic decrease in ethanol content even for the case of aluminum foil packaging. It is thus apparent that the cyclosporin-containing pharmaceutical composition using propylene carbonate and poloxamer 124 as the hydrophilic cosurfactant, with the exclusion of ethanol, according to the present invention is superior to the preparation according to the prior art with respect to the storage stability of the preparation.

Experiment 3

Propylene glycol which contains an -OH group in its molecular structure and therefore is highly hygroscopic and hydrophilic, is distributed inside the capsule shell by the movement of water present in both the contents

and the gelatin capsule during the encapsulation and drying processes and, therefore, eventually permeates the capsule shell. Since the constitutional ratio of the contents greately varies during the early stages of manufacturing processes, the stability of the preparation cannot be ensured and reliable therapeutic effects cannot be obtained. Therefore, depending on what kind of hydrophilic cosurfactant is used in the cyclosporin preparation the stability of the soft capsule preparation is varied. The permeability to the gelatin shell to the hydrophilic cosurfactant used in the soft capsule according to the present invention was determined and compared with the permeability of shell to propylene glycol, transcutol, glycofurol or dimethylisosorbide, used as the hydrophilic cosurfactants in soft capsules according to the prior art. The content of the solvent in each soft capsule preparation was analyzed by gas chromatography and HPLC. In order to apply the same conditions to each preparation each solvent and Cremophor RH40 were mixed in the ratio of 3:7. A constant amount of the sample was taken at regular intrevals and then analyzed. The test results and analytical conditions are given in the following Table 6.

A) Dimethylisosorbide

Column : Ultra 2 ; Column temperature : 230℃ ; Detector : FID ; Detector temperature : 270℃ ; Injection temperature : 275℃ ; Carrier gas : He ; Injection volume : 5㎕ ; Internal standard : octyl alcohol

B) Propylene glycol

Column : 10% PEG 20M ; Column temperature : 160℃ ; Detector : FID ; Injection temperature : 200℃ ; Carrier gas : N_2 ; Injection volume : 1㎕ ; Internal standard : pentadecanoic acid methyl ester

C) Transcutol

Column : Ultra 2 ; Column temperature : 230℃ ; Detector : FID ; Detector temperature : 270℃ ; Injection temperature : 270℃ ; Carrier

gas : He ; Injection volume : 5㎕ ; Internal standard : pentadecanoic acid methyl ester

D) Glycofurol

Column : Ultra 2 ; Column temp erature : 230℃ ; Detector : FID ; Detector temperature : 270℃ ; Injection temperature : 270℃ ; Carrier gas : He ; Injection volume : 5㎕ ; Internal standard : pentadecanoic acid methyl ester

Table 6

Change in the content of hydrophilic cosurfactant in the soft capsule preparations in course of time

Preparations	Solvent	Change of the content of hydrophilic cosurfactant (wt%, day)						
		0	5	15	30	60	90	120
Test preparation	Propylene carbonate	30.1	29.8	28.6	28.4	28.7	27.4	28.0
Comparative preparation	Dimethylisosorbide	30.0	28.2	29.1	28.7	28.0	26.6	25.8
	Propylene glycol	29.9	21.9	22.8	21.0	22.4	21.5	19.5
	Transcutol	30.1	22.1	23.1	21.9	22.1	21.7	20.3
	Glycofurol	30.0	24.4	21.0	23.5	21.0	20.7	20.4

From the result given in the above Table 6, it can be seen that in comparison to the hydrophilic cosurfactant used in the prior art, propylene carbonate used as the hydrophilic cosurfactant in the present invention is at least as stable as dimethylisosorbide and is more stable than propylene glycol, transcutol and glycofurol, and therefore, is retained at the initial content.

Since propylene carbonate, which is used in the present invention, does not cause any change in the constitutional ratio of the composition, the stability and reliability of preparation produced using such a cosurfactant component is better than that of the prior preparations.

Experiment 4

Comparative test for cyclosporin bioavailability of the composition of the present invention (test preparation) and a commercialized composition (comparative preparation):

Test preparation :

Component	Content (㎎/Cap.)
Cyclosporin	100.0
Propylene carbonate	150.0
Poloxamer 124	70.0
Cremophor RH40	370.0
Sefol 880	200.0
Mono-/di-glyceride	120.0
Tocopherol	3.0
Total	1013.0

Comparative preparation : Sandimmun Neoral® 100㎎

A) Test method

Six(6) dogs (male, body weight 11.0-15.0㎏) were used as the test animals and divided into two groups such that each group contains three dogs. The test was conducted in the manner of a crossover test method at intervals of two weeks during which the preparation is not administered. For the 18 hours preceding administation of both the test and comparative preparations, preceding the test animals were strictly prohibited from taking any food except water. In this test, each dog received the preparation in an amount

corresponding to 100㎎ as cyclosporin and then 50㎖ of water. 4 hours after administration of the preparation, the test animals were allowed to take a solid food. Before administration of the preparations blood for a blank test was taken. 2㎖ of blood was taken from each dog's abdominal vein at scheduled intervals after administration of the preparations. The blood thus obtained was stored in a refrigerator at -18℃ and then subjected to RIA.

B) Result

As the result of administration of the test and comparative preparations to 6 dogs according to the above method, the AUC and blood level of cyclosporin for each preparation are given in the following Table 7.

Table 7

AUC of the composition of the present invention and the commercial composition after oral administration

	Comparative preparation	Test preparation
A	2489	2690
B	2684	2456
C	2563	2538
D	2304	2381
E	2373	2568
F	2597	2630
G	2488	2501
Average	2499.7	2537.7

As can be seen from the result described in the above Table 7, the composition of the present invention shows a substantially comparable

bioavailability in dogs to the commercial comparative composition containing cyclosporin. Since the preparation according to the present invention is equivalent to the known commercial preparation, as measured by absorption of the active ingredient, it solves the problems inherent in the prior art preparations.

Experiment 5

Determination of the bioequivalence of the preparation according to the present invention (test preparation) and the cyclosporin-containing commercial preparation (comparative preparation) in human subjects:

The bioequivalence of the preparation according to the present invention (test preparation) and the cyclosporin-containing commercial preparation (comparative preparation) was determined as follows after administration to human subjects.

In this test, 20 to 28 years old 24 healthy adult men who did not take general medicine in recent days were included. First, the volunteers were randomly divided into two groups of 12 men each, and subjected to a crossover test with a 7 day interval. They each received an identical meal the evening before dosing and fasted from 12 hours before until 4 hours after administration of drug. 4 hours after administration of the preparation, the standard meal and water were provided. The soft capsule prepared according to Example 2-C was used as the test preparation and the commercial product Sandimmun Neoral® was used as the comparative preparation. The test preparation and the comparative preparation were each administered in the amount of 200㎎ of cyclosporin per person. Venous blood samples for the assay of cyclosporin in whole blood were obtained before dosing and at scheduled time intervals after dosing. The blood thus obtained was stored in a refrigerator until it was analysed. Concentrations of cyclosporin A were analyzed using radioimmunoassay and AUC was calculated according to a trapezoidal method. The bioavailability of each preparation is given in the following Table 8 on the basis of the item for evaluation of

bioequivalence and the curve showing blood level of cyclosporin is depicted in Figure 4.

Table 8

Bioavailability of the test preparation of the present invention and the comparative preparation

Parameters	Comparative preparation (A)		Test preparation (B)		P (B/A)**
	Mean	S.E.*	Mean	S.E.	
$AUC_{(0-24hr)}$ (ng · hr/mℓ)	5379.2	194.1	5370.2	176.2	0.99
C_{max} (ng/mℓ)	1243.4	35.2	1208.9	28.6	0.97
T_{max} (hr.)	1.6	0.1	1.6	0.1	1.0

Note) * S.E. : standard error

** P(B/A) : Ratio of average of the test preparation to the average of the comparative preparation

As can be shown from Table 8 and Figure 4, the cyclosporin- containing pharmaceutical composition using propylene carbonate and poloxamer 124 as the hydrophilic cosurfactant according to the present invention shows a substantially equivalent absorption pattern of cyclosporin in comparison to the commercial preparation according to the prior art. In addition, in the test preparation the standard error for blood concentration parameters is less than that of the comparative preparation. Therefore, in comparison with the comparative preparation, the test preparation forms a better microemulsion in the gastro-intestinal tract and is more uniformly absorbed.

From the results of experiments as mentioned above, it is apparent that the cyclosporin-containing pharmaceutical composition according to the present invention help to ensure a reliable therapeutic pharmacological

effect at least as good as that of the prior preparation and mitigates many of the shortcomings of the prior preparations.

WHAT IS CLAIMED IS :

1. A cyclosporin-containing pharmaceutical composition which comprises :

(1) cyclosproin as an active ingredient;

(2) propylene carbonate as a hydrophilic cosurfactant;

(3) either a medium chain triglyceride or a mono- and di- glyceride or a mixture of the two as an oil component; and

(4) a surfactant.

2. The cyclosporin-containing pharmaceutical composition according to claim 1 wherein cyclosporin is cyclosporin A.

3. The cyclosporin-containing pharmaceutical composition according to claim 1 wherein the hydrophilic cosurfactant additionally contains a pharmaceutically acceptable polyoxyethylene-polyoxypropylene block copolymer.

4. The cyclosporin-containing pharmaceutical composition according to claim 3 wherein the polyoxyethylene-polyoxypropylene block copolymer is Poloxamer 124.

5. The cyclosporin-containing pharmaceutical composition according to claim 3 wherein the hydrophilic cosurfactant is a mixture of propylene carbonate and polyoxyethylene-polyoxypropylene block copolymer in the mixing ratio of 1:0.1-5 on the basis of weight.

6. The cyclosporin-containing pharmaceutical composition according to claim 5 wherein the hydrophilic cosurfactant is a mixture of propylene carbonate and polyoxyethylene-polyoxypropylene block copolymer in the mixing ratio of 1:0.1-1 on the basis of weight.

7. The cyclosporin-containing pharmaceutical composition according to claim 1 wherein the medium chain triglyceride is a triglyceride of a C_8-C_{10} fatty acid.

8. The cyclosporin-containing pharmaceutical composition according to claim 1 wherein the mono- and di-glyceride is a mixture of glycerol mono- and di-esters of a fatty acid.

9. The cyclosporin-containing pharmaceutical composition according to claim 1 wherein the oil component is a mixture of a medium chain triglyceride and mono- and di-glyceride in the mixing ratio of 1:0.1-1 on the basis of weight.

10. The cyclosporin-containing pharmaceutical composition according to claim 9 wherein the oil component is a mixture of medium chain triglyceride and mono- and di-glyceride in the mixing ratio of 1:0.1-0.5 on the basis of weight.

11. The cyclosporin-containing pharmaceutical composition according to claim 1 wherein the surfactant is one or more surfactants selected from the group consisting of polyoxyethylene glycolated natural or hydrogenated vegetable oils, polyethylene glycol mono- and di-fatty acid esters, polyoxyethylene sorbitan fatty acid ethers, polyoxyethylene fatty acid esters, polyoxyethylene alkyl ethers, and transesterification products of natural vegetable oil triglyceride and polyalkylene polyol.

12. The cyclosporin-containing pharmaceutical composition according to claim 11 wherein the surfactant is selected from the group consisting of polyoxyethylene glycolated natural or hydrogenated vegetable oils and transesterification products of natural vegetable oil triglyceride and polyalkylene polyol.

13. The cyclosporin-containing pharmaceutical composition according to claim 12 wherein the surfactant is a mixture of polyoxyethylene glycolated natural or hydrogenated vegetable oils and transesterification products of natural vegetable oil triglyceride and polyalkylene polyol, in the constitutional ratio of 1:0.1-1 on the basis of weight.

14. The cyclosporin-containing pharmaceutical composition according

to claim 13 wherein the surfactant is a mixture of polyoxyethylene glycolated natural or hydrogenated vegetable oils and transesterification products of natural vegetable oil triglyceride and polyalkylene polyol, in the constitutional ratio of 1:0.1-0.5 on the basis of weight.

15. The cyclosporin-containing pharmaceutical composition according to claim 1 wherein said cyclosporin, said hydrophilic cosurfactant, said surfactant and said oil component are present in the constitutional ratio of 1 : 0.5-5 : 1-7 : 0.5-5 on the basis of weight.

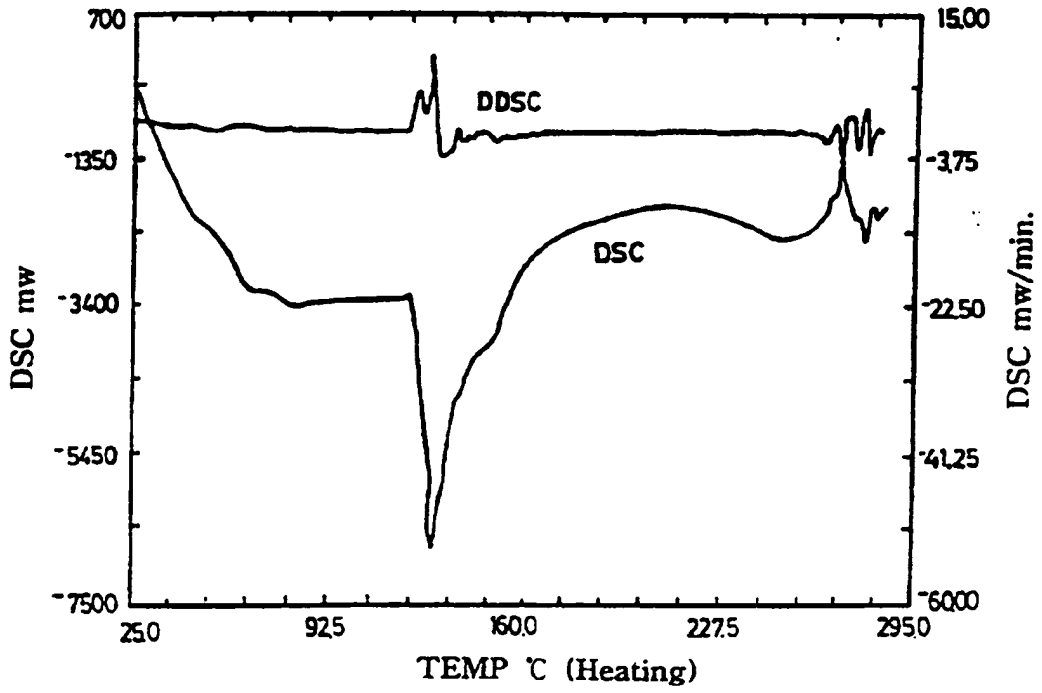
16. The cyclosporin-containing pharmaceutical composition according to claim 15 wherein said cyclosporin, said hydrophilic cosurfactant, said surfactant and said oil component are present in the constitutional ratio of 1 : 1-3 : 3-7 : 1-3 on the basis of weight.

17. The cyclosporin-containing pharmaceutical composition according to claim 1 wherein it further contains one or more pharmaceutically acceptable additives selected from the group consisting of antioxidant, preservatives and stabilizers.

18. The cyclosporin-containing pharmaceutical composition according to claim 1 wherein it is formulated as an orally administrable preparation.

19. The cyclosporin-containing pharmaceutical composition according to claim 18 wherein the orally administrable preparation is a soft capsule, a hard capsule sealed with a gelatin bending at the conjugated portion, or an oral liquid preparation.

Figure 1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TEMP ℃ (Heating)

Figure 2

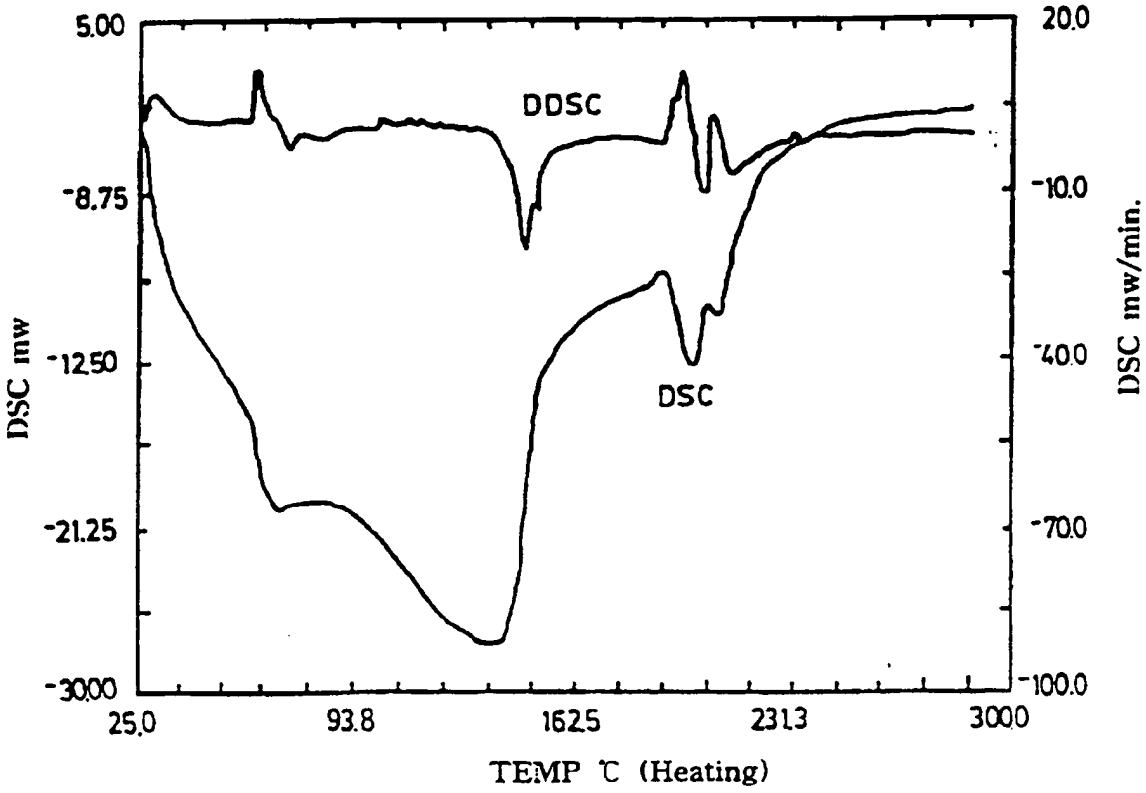
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Figure 3

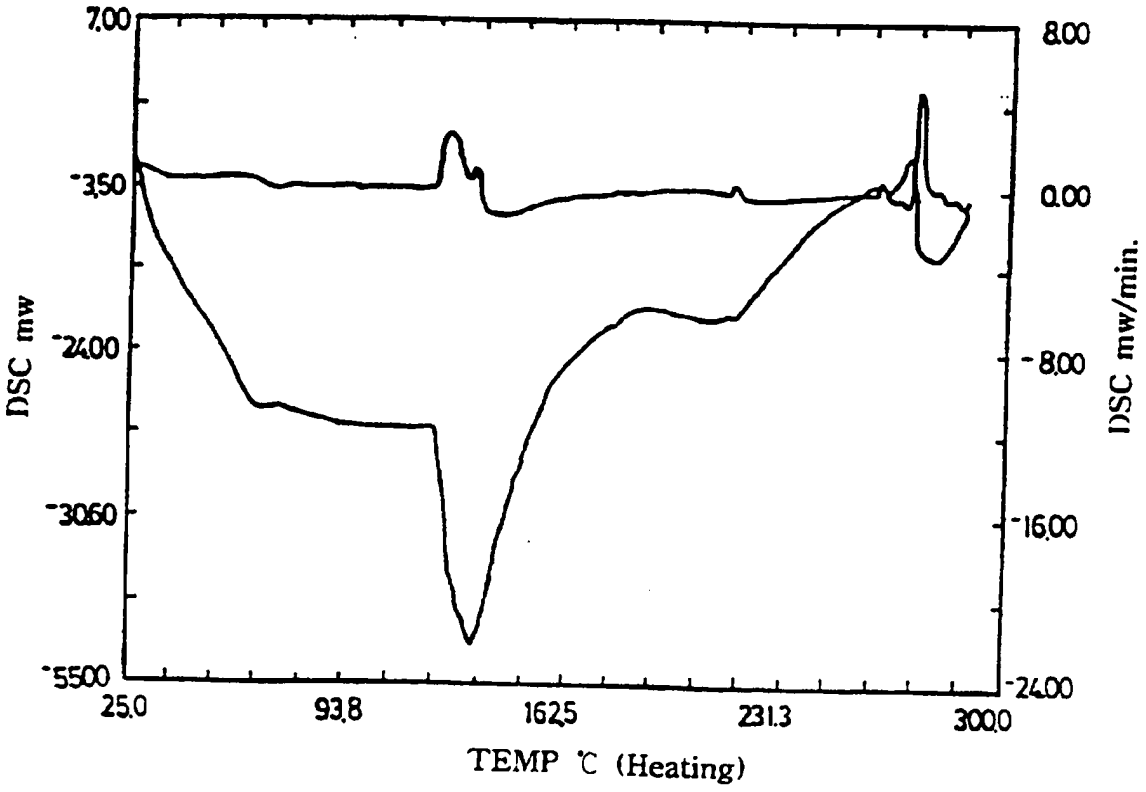
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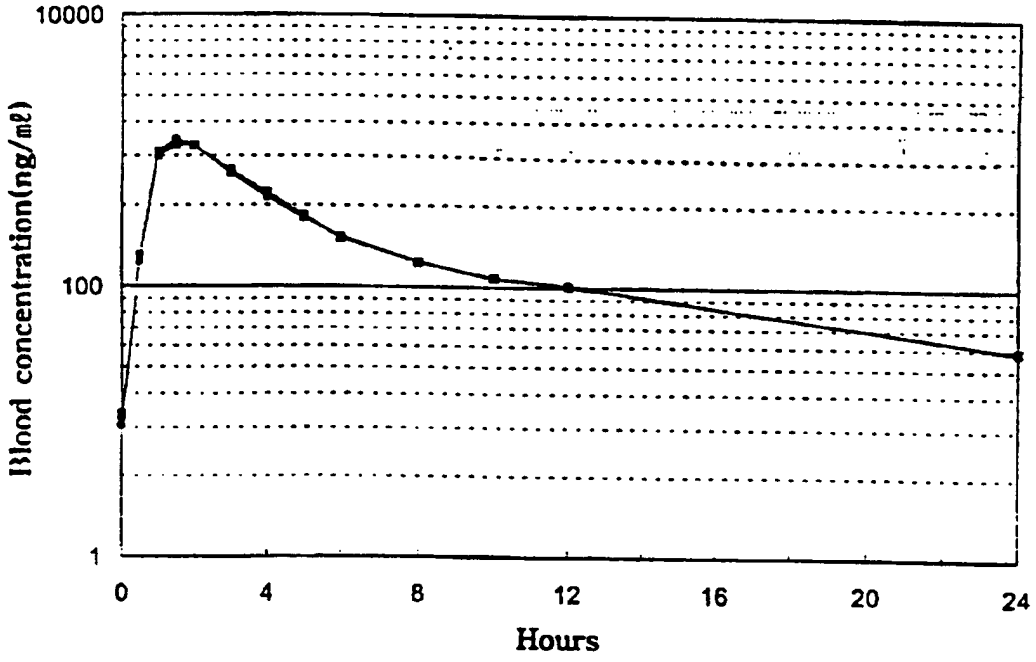
Figure 4



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 97/00098

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: A 61 K 38/13

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: A 61 K 38/13

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPIL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database WPIL on Questel, week 38, London, Derwent Publications Ltd., AN 95-290 317, & JP 7-188 046 A (LTT KENKYUSHO K), abstract.	1,2
A	Database WPIL on Questel, week 40, London, Derwent Publications Ltd., AN 94-322 107, & JP 6-247 869 A (DOT Y), abstract.	1
A	EP 0 711 550 A1 (HANMI PHARM. IND. CO., LTD.) 15 May 1996 (15.05.96), abstract; claims 1-3.	1,2,7,8,18,19
A	EP 0 539 319 A2 (SANDOZ LTD.) 28 April 1993 (28.04.93), claim 1.	1

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
04 August 1997 (04.08.97)	19 August 1997 (19.08.97)
Name and mailing address of the ISA/AT AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer Wolf Telephone No. 1/53424/436

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 97/00098

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